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The invention concerns an adhesive film, which exhibits a certain adhesion at the tooth surface or at the gums and in water soluble or pourable is and is stored as remineralisierender active substance into the one purify-hasty calcium salt severe-soluble in water.

The care and healthy attitude of the teeth cleaning agents do not only become such as z. B. Zahnpasten or mouth water uses. Also Lutschpastillen or chewing rubber preparations, which have a longer period spent in the mouth, are suitable for bringing certain active substances to the Zahnfleich or to the tooth surface. Finally already one suggested equipping adhesive films, which cling on the gums or on the tooth surface, with active substances against Karies or Parodontitis.

As one of the first stages of the Zahnkaries lesions in the Zahnschmelz and open Dentinkanälchen (so-called become. Tomes of pit) observes, which results from solution procedures under the influence of acid-forming bacteria. The opening of the Dentinkanäle makes itself z. B. by tooth neck sensitivity in relation to variations in temperature noticeably. While by additives of desensitizing active substances the painful symptoms are only fought, one tried by additives, which reduce the apatite solubility, already, to prevent the formation of such tooth surface lesions. In more recent time suggestions were also already made to reduce existing damage by remineralisierende dental care means. Thus became from Chow and Brown (in J. Dent. Res., 54 (1975), 65-70) suggested using Dicalciumphosphat dihydrate to the Remineralisation of the Dentins. Made of US 4.097.588 a mouth water with remineralisierender effect was well-known, which was satisfied with CaHPO4.2H2O.

In EP 0,165,454 B1 hydroxyl apatite or fluorine apatite in purify-hasty form (under 4 micrometers particle diameters) is suggested as component of dental care means.

From EP 0,381,193 a2 are foils for application at the mouth mucous membrane well-known, the one topischen active substance, z. B. also Natriumfluorid or Kaliumnitrat, contained can.

WHERE 95/33441 A1 describes phosphate-free compositions, the purify-hasty (colloidal) metal connections, z. B. the yttrium, cerium, aluminum or zirconium for the treatment of hyper+sensitive teeth to be contained and also in the form of mouth sticking plasters be appliziert are.

There was therefore the task, an effective application form for those remineralisierend working calcium salts, in particular the phosphates, fluorides, to find fluorine phosphates as well as hydroxyl and fluorine apatite some local Remineralisation of the damaged Zahnschmelzes effectuation to find.

This task according to invention solved by Dental adhesive film to local, remineralisierenden dental treatment, consisting of in water soluble or pourable, to tooth adherent carrier material and in it stored active substances, whereby as active substances a purify-hasty calcium salt, selected from phosphates, severe-soluble in water, fluorides, fluorine phosphates and mixtures of it, which can cover if necessary also hydroxyl, carbonate or chloride ions, is contained.

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The transparency can consist thereby of any firm, flexible material pourable soluble in water or. Suitable materials are prefer natural or synthetic polymers, which are plasticized with water and/or water-mixable solvents. An example of such a material is z. B. in accordance with US 3.444.858 a gel plasticized by water and Glycerin. Further examples of suitable carrier materials are in accordance with WHERE 00/18365 A1 z. B. Pullulan, Hydroxypropylcellulose, Hydroxyethylcellulose, Hydroxypropyl methylcellulose, Carboxymethylcellulose, Natriumalginat, Xanthan Gum, Traganth, Guar, acacia Gum, gum Arabicum, amyl eye, Hydroxypropyl strength, Dextrin, Pektin, Chitin, Chitosan, Levan, Collagen, Zein, glows, Sojaprotein, Casein, Polyvinylpyrrolidon, polyvinyl alcohol, Polyethylenglycol, Polyacrylsäure, Methylmethacrylat/acrylic acid copolymer and mixtures of it. In a preferential practice of the invention a water-soluble or water-pourable natural or synthetic polymer material, selected contained of the acryl or Methacrylsäure, polyvinyl alcohol, teilverseiftem Polyvinylacetat, Polyvinylpyrrolidon and mixtures from vegetable and mikrobiellen Gummen, is gel, Celluloseethern, copolymers from acryl or Methacrylsäure and esters of it as carrier component.

During the composition of the carrier material it depends above all on the fact that the active substances are set free controlled during a longer period from the carrier that thus the carrier material in the mouth under the effect of the saliva liquid does not disintegrate too rapidly or too rapidly dissolves and the active substance is swallowed, before it at the tooth or gums came to the effect.

One can retard disintegration or dissolution of the carrier material by different measures and control the release of the active substances thereby purposefully. Such measures are z. B. cross-linking water-soluble polymers, the additive of less water-soluble polymers, the additive of hydrophoben components, z. B. Magnesium stearate, or, as in WHERE 99/04764 A1 suggested, the use of with Gerbsäuren or Tannin interlaced proteins or Celluloseethern.

The production of transparencies from a suitable carrier material effected in well-known procedures, by manufacturing a solution polymers or the polymer mixture, the active substances in it solves or disperses and this solution or dispersion in thin layer on an not-adherent, z. B. one with silicone coated, document dries. After the evaporation of the solvent the

finished foil of the document can be replaced and be cut if necessary into one for the application at the teeth suitable size.

When in water severe-soluble calcium salt are such salts are understood, those with 20 DEG C to less than 0.1 Gew. - % (1 g/l) in water are soluble. Such suitable salts are z. B. Calciumhydroxyphosphat (Ca5 [OH (PO4) 3]) and/or. Hydroxyl apatite, calcium fluorine phosphate (Ca5 [F (PO4) 3]) and/or. Fluorine apatite, fluorine-endowed hydroxyl apatite of the composition Ca5 (PO4) 3 (OH, F) and calcium fluoride (CaF2) and/or. Fluorit or fluor-spar as well as other calcium phosphates such as the, trichloroethylene or Tetracalciumphosphat (Ca2 P2O7, Ca3 (PO4) 2, Ca4P2O9, Oxyapatit (Ca10 (PO4) 6O) or nonstoichiometric hydroxyl apatite (Ca5-1/2 (x+y) (PO4) 3-x (HPO4) x (OH) 1-y).

When remineraliserender active substance is suitable prefers a purify-hasty calcium salt severe-soluble in water, which is selected from hydroxyl apatite, fluorine apatite and mixtures of it since the tooth material, whose restoration is the goal of the Remineralisation, exists to approximately 95% made of hydroxyl apatite.

When particularly favourably have themselves such little water-soluble calcium salts proven, which prove a middle particle refinement of 10-300 Nm (nanometers). As particle refinement the diameter of the particles is to be understood here toward their largest linear extension. The middle particle refinement refers to an volume-averaged value. Such calcium salts leave themselves to z. B. after from DE 198 58 662 A1 procedures in form admitted of rod-shaped Primärteilchen with thicknesses of 5-50 Nm and lengths of 10-150 Nm manufacture.

During the biological developing process of the Zahnschmelzes as well as the supporting fabric of the bones hydroxyl apatite deposits itself in arranged way to the protein matrix in the tooth or bone, which consists predominantly of Kollagen. The training of the hard and strong mineral structure steered thereby by so-called matrix proteins, which are formed from Kollagen and further proteins, to the Kollagen to deposit itself and so a controlled mineralizing process, which so-called biomineralization, to cause.

Proteins serve also as Schutzkolloide, which are adsorbed to the surface of the nano-particles and these from a coagulation and a dye to prevent and the crystal growth down slow. Also with the Remineralisation of the damaged tartar it depends on the fact that no uncontrolled crystal growth takes place, which could train only a loose crystalline structure. Rather the crystal growth should run off braked and by proteins as Schutzkolloid controlled, so that a close and sufficiently firm crystalline structure can be formed.

In a preferential execution the Dental adhesive film according to invention contains further a protein component, selected from proteins, protein dismantling products and derivatives of proteins or protein dismantling products.

As proteins thereby all proteins come independently of their origin infrage, thus both animal and vegetable proteins. Suitable ones animal proteins are z. B. Kollagen, Fibroin, Elastin, Keratin, albumin and Casein. Suitable ones vegetable proteins are z. B. Wheat and wheat germ proteins (glows), rice protein, Sojaprotein, oats protein, pea protein, almond protein and potato protein. Also single-celled organism proteins such as z. B. Yeast protein or bacteria proteins is suitable.

Preferential according to invention proteins are animal products such as Kollagen, Keratin and Casein.

In accordance with a further preferential execution form the protein can originate from a vegetable or marine source.

As protein dismantling products such products are understood, which are available by hydrolytic, oxidative or reductive exploitation from water-insoluble proteins to Oligo and Polypeptidstrukturen with lower molecular weight and with an improved water solubility.

The hydrolytic dismantling of water-insoluble proteins is the most important dismantling method; it can take place under the catalytic influence from acids, alkalis or from enzymes. Preferentially suitably are above all such protein dismantling products, which continue to be diminished not as for the acquisition of the water solubility necessarily.

Among the little diminished protein hydrolysates for example in the context of the available invention the preferred gel, which can exhibit mol masses within the range of 15000 to 250000 D, ranks. Gel is a Polypeptid, which is won primarily by hydrolysis by Kollagen under sour (gel type A) or alkaline (gel type B) conditions. The gel strength of the gel is proportional to its molecular weight, D. h., a more strongly hydrolyzed gel results in low viscose rayon a solution. The gel strength of the gel is indicated in Bloom numbers. During enzymatic splitting of the gel the polymer size is strongly degraded, which leads low Bloom numbers too much.

By derivatives of proteins and protein dismantling products chemically modified proteins or protein hydrolysates are understood, the z. B. by acylation of free amino groups, by accumulation of ethyl or propylene oxide and hydroxyl, revision modification NO or groups of carboxyls or by alkylation of hydroxyl groups of the protein or protein dismantling product or a hydroxyalkyl derivative of it, z. B. with Epoxypropyl trimethylammoniumchlorid or 3-Chlor-2-hydroxypropyl tri methyl ammonium chloride, is available.

In a particularly preferred execution the protein component is selected made of gel, Casein, their hydrolysates and mixtures of it. The Dental adhesive film according to invention knows z. B. as carrier material predominantly from a protein component, z. B. of gel or Kollagen, consist. If however as carrier material differently material, z. B. a plant Gum, a single-celled organism bio polymer (Xanthan Gum, Pullulan), a cellulose or a Stärkeether, a Polyvinylpyrrolidon or a mixture from Celluloseether, Polyvinylacetat and Polyacrylsäure are used, then prefers a protein component should therein in a quantity of at least 1 Gew. - %, prefers from 1-20 Gew. - % contained its.

A further particularly preferential execution form consists of the fact that as active substance a Kompositmaterial from the calcium salt severe-soluble in water and a protein component, selected from proteins, is contained protein dismantling products and derivatives of proteins or protein dismantling products. As Kompositmaterialien thereby group materials are understood, which the severe-soluble calcium salts and the protein components to cover and microscopically heterogeneous, appearing macroscopically however homogeneous aggregates to represent, in which to the stand of the protein component associates the primary particles of the calcium salts to be present. The portion of the protein components in such Kompositmaterialien lies between 0,1 and 60 Gew. - % prefers however between 1,0 and 20

Gew. - %, related to the weight of the Kompositmaterials.

The production of Kompositmaterialien from hydroxyl apatite and Kollagen becomes z. B. of R. Z. Wang et al., J. Mould. Sci. Lett. 14 (1995), 490 described. The there available hydroxyl apatite particles wear a particle refinement of 2-10 Nm and to belong therefore to the range of the amorphous or partial X-ray-amorphous materials. Hydroxyl apatite nano-particles, which exhibit a clearly recognizable crystalline morphology, are better suitable, whose particle refinement lies therefore within the range of 10-300 Nm. Kompositmaterialien are likewise better suitable, with which the purify-hasty severe-soluble calcium salts with particle refinement of 10-300 Nm as well as purify-hasty proteins, protein hydrolysates or derivatives of it form a spatial structure in such a manner that the purify-hasty calcium salts of the protein structure are supported, these quasi spatially illustrate. From such prefers suitable nano-individual calcium salts and protein components existing Kompositmaterialien lead to a particularly effective biomineralization.

Suitable according to invention Kompositmaterialien can be made by precipitation of aqueous solutions of water-soluble calcium salts with aqueous solutions water-soluble phosphates and/or fluoride salts in presence of protein components.

This preferably takes place in the way that the protein components in pure, solved or colloidal form of the alkaline aqueous phosphate and/or fluoride saline solution or the alkaline solution of the calcium salt before the precipitation reaction are attached. Alternatively the protein components in pure, solved or colloidal form can become submitted and afterwards successively in arbitrary order or simultaneous with the alkaline calcium saline solution as well as the alkaline phosphate and/or fluoride saline solution staggered.

With the manufacture procedures joining the individual components can take place in principle in all possible orders. As alkalization means prefers ammonia used. With all precipitation reactions the pH value is to be to this kind to the gefällten system above pH = 5.

A further variant of the manufacture procedure consists of the fact that one accomplishes the precipitation from a sour solution of a water-soluble calcium salt as well as a stoichiometric quantity of a water-soluble phosphate and/or fluoride salt or from a sour solution by hydroxyl apatite with a pH value below 5, preferentially at a pH value below 3, by raising of the pH value with aqueous alkali or ammonia to a value above 5 in presence of the protein components.

A further procedure variant consists of the fact that one prefers nano-individual calcium salts in pure or dispersed form or by precipitation reactions from aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate and/or fluoride salts manufactured dispersions of nano-individual calcium salts with the protein components, the latters in solved or dispersed form, staggered, whereby with the addition any sequence can be selected.

Preferred the solution or dispersion of the protein component is submitted and a dispersion of the nano-individual calcium salt is added.

At all procedures, in the process of those a precipitation of apatite takes place, recommends it, the pH value above 5, to hold itself.

With all manufacture procedures mentioned the developing dispersion of the Kompositmaterials knows as required through the specialist well-known procedures, like z. B. Filtration or Zentrifugation, from the solvent and the remaining ingredients of the reaction mixture separated and by following drying process, z. B. by freezing drying process, in solvent-free form to be isolated.

As solvents with all production processes prefers water used, however also organic solvents can such as z in individual steps of the production. B. Alcohols with 1 to 4 C-atoms or Glycerin to be used.

In a special execution form of the invention the purify-hasty calcium salt primary particles or the purify-hasty calcium salt primary particles available in the Kompositmaterialien can be coated of one or more surface modification means.

Thus for example the production of Kompositmaterialien in such cases can be facilitated, with which the nano-individual calcium salts can be dispersed more severe. The surface modification means is adsorbed to the surface of the nano-particles and altered it such that the dispersion barness of the calcium salt increases and the dye of the nano-particles is prevented.

Beyond that the structure of the Kompositmaterialien as well as the loading of the protein component can be affected with the nano-individual calcium salt by a surface modification. In this way it is possible with the application of the Kompositmaterialien in Remineralisationsprozessen to exert influence on the process and the rate of the Remineralisationsprozesses.

By surface modification means materials are to be understood, which adhere to the purify-hasty particle at the surface physically, with these however chemically do not react. The individual molecules of the surface modification means adsorbed at the surface are essentially free from inter+molecular connections among themselves. By surface modification means in particular dispersing agents are to be understood. Dispersing agents are well-known the specialist also under the terms Tenside and Schutzkolloide. Suitable Tenside or polymere of Schutzkolloide can be taken from the German patent application DE 198 58 662 A1.

The production of the Kompositmaterialien according to invention, in which the primary particles of the calcium salts are surface-modified, can take place in similar precipitation procedures as managing described, whereby however the precipitation of the nano-individual calcium salts or the Kompositmaterialien takes place in present one or several surface modification means.

Preferred first by a precipitation reaction between aqueous solutions by calcium salts and aqueous solutions by phosphate and/or fluoride salts in presence of the surface modification means the surface-modified nano-individual calcium salts one produces. These can be cleaned afterwards by Begleitprodukten of the reaction mixture, z. B. by restricting under reduced pressure and following dialysis. Additionally a dispersion of the surface-modified calcium salt with a Feststoffanteil can be manufactured by taking the solvent off according to desire. Becomes subsequently, by addition of the protein components in pure, solved or colloidal form, whereby again the sequence of the addition is

uncritical, and if required post-reaction prefers the Kompositmaterial from calcium salt and protein components surface-coated at increased temperature, within the range between 50 and 100 DEG C and for one duration from 1 to 100 minutes, in an educated manner.

For the production of the Dental adhesive film according to invention the active substance, thus the purify-hasty calcium salt severe-soluble in water or prefers the Kompositmaterial from the severe-soluble calcium salt and a protein component, the still liquid solution of the carrier material in water or aqueous alcohol added. In addition the active substance can be used as water and solvent-free powder or also as aqueous or aqueous-alcoholic dispersion. Finally the dispersion in thin layer on an not-adherent document, received thereby, is dried. The additional amount depends thereby on how much by the active substance in adhesive film is to be contained of the finished Dental. In a preferential practice of the invention is the active substance in a quantity of 0,1-10 Gew. - % in the ready for use Dental adhesive film contain.

Additionally to according to invention contained the remineralisierenden, purify-hasty Caciumsalz severe-soluble in water further active substances, which are compatible with the carrier material for the health of the teeth or the gums favorably and, can be contained. Such further active substances are z. B.

- Karieshemmende fluorine compounds, z. B. Natriumfluorid, tin fluoride or sodium mono fluorine phosphate,
- Anti-tartar active substances, z. B. Organophosphonate such as 1-Hydroxyethan-1,1 diphosphonsäure, Phosphonopropan-1,2,3-tricarbonsäure (well salts), 1 - Azacycloheptan-2,2-diphosphonsäure (well salt),
- Desensitizing active substances such as z. B. Kaliumnitrat or carnation oil (Eugenol),
- Wundheilende and entzündungshemmende materials such as z. B. Allantoin, urea, Azulen, chamomile active substances, Rhodanid,
- Deodorierende and antimicrobial materials such as z. B. Chlorhexidin, Hexetidin, Bromchlorophen.

Further aids to the improvement of the organoleptischen characteristics can be likewise contained, z. B.

- Flavour oils such as z. B. Pfefferminzöl, Krauseminzöl, Eukalyptusöl, anise oil, Fenchelöl, Kümmelöl, fruit flavour and synthetic flavour oils,
- Sweet means such as z. B. Saccharin sodium, Acesulfam k, Aspartame TM, sodium Cyclamat, Stevioside, Thaumatin, Sucrose, lactose, Maltose, Fructose or Glycyrrhicin,
- Coloring materials and pigments.

The following examples are to describe the invention article more near:

Examples

1. Production of protein solutions and/or. - dispersions

1,1 gel type A

10 g gel type A (gel won by sour hydrolysis of pig skin) were once boiled up with 100 ml water staggered and by means of microwave.

1,2 gel type A and Casein

10 g gel type A were once boiled up with 100 ml water as well as 10 ml the projection and afterwards of a Caseinlösung staggered centrifuged satisfied with 20 DEG C with 5000 RPM and afterwards by means of microwave.

1,3 hydrolysate of gel type A

10 g gel type A became with 100 ml water as well as the alkaline Protease Savinase (manufacturer: Novo Nordisk) in an employment concentration of 0,005% enzyme dry substance, related to the dry substance of the Gelantine, staggered. After 20 h agitating with 20 DEG C was once boiled up by means of microwave.

1,4 hydrolysate of gel type A and Casein

10 g gel type A and 1 g Casein became with 100 ml H2O staggered, over night at ambient temperature with alkaline Protease Savinase (manufacturer: Novo Nordisk) in an employment concentration boiled up by 0,005% enzyme dry substance, related to which dry substance of the protein components hydrolyzes, then once in the microwave and afterwards filters.

1,5 gel type B

10 g gel type B (gel won by alkaline hydrolysis of cattle skin) were once boiled up with 100 ml water staggered and by means of microwave.

1,6 gel type B and Casein

10 g gel type B were once boiled up with 100 ml water as well as 10 ml the projection and afterwards of a Caseinlösung staggered centrifuged satisfied with 20 DEG C with 5000 RPM and afterwards by means of microwave.

1,7 hydrolysate of gel type B

10 g gel type B became with 100 ml water as well as the alkaline Protease Savinase (manufacturer: Novo Nordisk) in an employment concentration of 0,005% enzyme dry substance, related to the dry substance of the gel, staggered. After 20 h agitating with 20 DEG C was once boiled up by means of microwave.

1,8 hydrolysate of gel type B and Casein

10 g gel type B and 1 g Casein became with 100 ml H2O staggered, over night at ambient temperature with alkaline Protease Savinase (manufacturer: Novo Nordisk) in an employment concentration hydrolyzed by 0,005% enzyme dry substance related to the dry substance of the protein components, then once in the microwave boiled up and afterwards

filters.

2. Production of Kompositmaterialien by precipitation reactions in presence of the protein components

2,1 Kompositmaterial from hydroxyl apatite and gel type A

2,21 g calcium chloride were solved in 137 ml demineralized water, kept at a moderate temperature on 25 DEG C and with 25 Gew. - %iger aqueous ammonia solution on pH = 11 adjusted. Under strong agitating afterwards 20 was added ml, to the protein solution manufactured warmed up in the Wasserbad to 30-40 DEG C after example 1,1. In the connection an aqueous solution was course-dripped of 1,58 g Diammoniumhydrogenphosphat in 26 ml demineralized water, which kept at a moderate temperature on 25 DEG C and with ammonia solution on pH = 11 adjusted was. slowly within 1 h. The precipitation of the Kompositmaterials took place. The pH value was to starts of the Zutropfzeit about 10,4 and became by Nachdosierung of ammonia solution at a value of approx. 10 maintained. After 20 h response time (25 DEG C, under agitating) had dropped the pH value of the aqueous suspension on 9,5. The failed Kompositmaterial with 5000 RPM abzentrifugiert with approx. 30-40 DEG C warm demineralized water washed and freezingdried. One received 2.2 g Kompositmaterial, whose elementary analysis resulted in carbon content of 2,3%; this corresponds to a content of protein material of 5,6 Gew. - %, related to the total quantity of the Kompositmaterials.

2.2-2.8 Kompositmaterialien from hydroxyl apatite and further protein components

In similar way as under example 2,1 one kept Kompositmaterialien from hydroxyl apatite as well as the protein components described under 1.2 to 1,8 described.

3. Production of Kompositmaterialien by training of dispersions of surface-modified calcium salts in protein components

3,1 Kompositmaterial from hydroxyl apatite and gel Bloom 300

First separated the solutions A and B were manufactured.

Solution A

25,4 g Calciumnitrat tetrahydrat and 8,50 g Diammoniumhydrogenphosphat in 100 g entionisiertem water was solved in each case. Both solutions were together-given under training of a white precipitation. After addition of 10 ml 37 Gew. - %iger HCl received one a clear solution.

Solution B

200 ml entionisiertes water, 200 ml 25 Gew. - %ige aqueous ammonia solution as well as 20 g of plan TAC acres TM 1200 were together-given and cooled down on 0 DEG C in the ice bath.

Under training of a hydroxyl apatite precipitation one gave solution A under strong agitating to solution B. After taking surplus ammonia off the dispersion was cleaned by means of dialysis. At the rotation evaporator one restricted the dispersion by determination of the separated quantity of water afterwards so far that the Feststoffanteil in the dispersion computes, as hydroxyl apatite, 7,5 Gew. - amounted to %.

This dispersion became at ambient temperature 100 ml g of an analogue example 1,1 manufactured 10 Gew. - %igen aqueous solution of gel Bloom 300 (manufacturers: Fluka) admitted, then on 80 DEG C warms up and at this temperature 5 minutes agitated. One let the mass under training of the Kompositmaterials with ambient temperature subsequently, solidify.

4. Production of Dental adhesive films

4,1 PVAc/HPC foil

A dispersion of the Kompositmaterials in aqueous alcoholic solution was manufactured by Polyvinylacetat and Hydroxypropylcellulose of the following composition.
< tb> < TABLE> Columns= 2>
< tb> < UCB AL=L> Wasser< SEP> 9 Gew. - %
< tb> Methanol< SEP> 80 Gew. - %
< tb> Kompositmaterial< SEP> 1 Gew. - %
< tb> < /TABLE>

The dispersion poured in 2 m thicken layer dried onto a silicone-coated document and. It became approx. 0.2 mm thick film receive, which was cut in 1 cm broad bands. 4,2 Gelatine-Folie
< tb> < TABLE> Columns= 2>
< tb> < UCB AL=R> 1.0 Gew. - %
< tb> < UCB AL=L> Ethanol< SEP> 45.0 Gew. - %
< tb> Wasser< SEP> 35.0 Gew. - %
< tb> Galloylgallussäure< SEP> 9.0 Gew. - %
< tb> < /TABLE>

The dispersion was poured and dried in 2 mm of thick layer onto a silicone-coated document. It became approx. 0.2 mm thick film receive, in approx. 1 cm broad bands was cut.